In vitro expansion of large numbers of highly potent tumor-reactive T cells appears a prerequisite for effective adoptive cell therapy (ACT) with autologous tumor-infiltrating lymphocytes (TIL) as shown in metastatic melanoma (MM). We therefore sought to determine whether renal cell carcinomas (RCC) are infiltrated with tumor-reactive T cells that could be efficiently employed for adoptive transfer immunotherapy. TILs and autologous tumor cell lines (TCL) were successfully generated from 22 (92%) and 17 (77%) of 24 consecutive primary RCC specimens and compared with those generated from metastatic melanoma. Immune recognition of autologous TCLs or fresh tumor digests was observed in CD8(+) TILs from 82% of patients (18/22). Cytotoxicity assays confirmed the tumoricidal capacity of RCC-TILs. The overall expansion capacity of RCC-TILs was similar to MM-TILs. However, the magnitude, polyfunctionality, and ability to expand in classical expansion protocols of CD8(+) T-cell responses was lower compared with MM-TILs. The RCC-TILs that did react to the tumor were functional, and antigen presentation and processing of RCC tumors was similar to MM-TILs. Direct recognition of tumors with cytokine-induced overexpression of human leukocyte antigen class II was observed from CD4(+) T cells (6/12; 50%). Thus, TILs from primary RCC specimens could be isolated, expanded, and could recognize tumors. However, immune responses of expanded CD8(+) RCC-TILs were typically weaker than MM-TILs and displayed a mono-/oligofunctional pattern. The ability to select, enrich, and expand tumor-reactive polyfunctional T cells may be critical in developing effective ACT with TILs for RCC. In summary, TILs isolated from primary RCC specimens could recognize tumors. However, their immune responses were weaker than MM-TILs and displayed a mono-/oligofunctional pattern. The ability to select and expand polyfunctional T cells may improve cell therapy for RCC. (C) 2018 AACR.